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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,913	LANDEGREN, ULF	
	Examiner	Art Unit	
	Sally A. Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 22-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 22-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 11/09/2004. Claims 1-21 have been canceled, and claims 22-32 have been added. Claims 22-32 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

THE FOLLOWING ARE NEW REJECTIONS NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 22, 26, 27, and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Nilsson et al.(Science, Vol. 265, pages 2085-2088 September 30, 1994).

With regard to claim 22, a cleavable, detectable function is broadly interpreted to include anything that is removable and detectable. For example, a nucleotide that is exonuclease-treated and detected is interpreted as meeting this claim limitation. Nilsson et al. teaches a method of detecting a target nucleic acid sequence in a sample by contacting the sample with a detectable probe to hybridize the probe to the target sequence, and detecting the hybridized probe, said

probe has two free nucleic acid end parts which are at least partially complementary to and capable of hybridizing to two at least substantially neighboring regions of the target sequence (Figure 4 description), comprising the following steps:

a) hybridizing the probe ends to the target sequence under hybridization conditions (Figure 4 description);

b) covalently connecting the ends of the hybridized probe with each other to form a circularized structure;(Figure 4 description)

c) cleaving the cleavable function (e.g. washing under denaturing conditions in this case) (Figure 4), characterized in that the probe is provided with a cleavable or dissociable detectable function (Figure 4 description), and the method comprising the further steps of:

d) separating detectable functions no longer linked to the solid phase (Figure 4 description);

e) detecting the presence and, if desired, location of the remaining probe as indicative of the presence of the target nucleic acid sequence (Figure 4 description).

With regard to claims 26 and 27, Nilsson et al. teaches that the detectable function is dissociable by being provided either on a further circularizable probe or on a target-specific probe (Figure 4 description).

With regard to claim 30, Nilsson et al. further teaches the performance covalent connection of the probe ends by enzymatic or chemical ligation (Figure 4 description).

With regard to claim 31, Nilsson et al. teaches the DNA or RNA as target molecule (Figure 4 description).

With regard to claim 32, Nilsson et al. teaches the immobilization of oligonucleotide probes as well as the target sequence to a solid phase (Figure 4 description).

Response to Arguments

Applicant's arguments filed 11/9/2004 have been fully considered but they are not persuasive. While applicant's summary of their invention and the subject matter depicted in the applied art on pages 7-8 is noted, applicant is reminded that only the claims define the invention and that furthermore, that limitations in applicant's arguments, specification etc cannot be read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, without a requirement for the methods particular, constituent steps mentioned on pages 7 and 8 for example, the art will be applied as broadly as the claims are written. The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*,415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111). Applicants first argue on page 8, that "contrary to the assertions of the official action, the probe disclosed by Nilsson et al. does not contain any cleavable function or dissociable detectable functions". However, applicant is reminded that with regard to claim 22, a cleavable, detectable function is broadly interpreted to include anything that is removable and detectable. For example, a nucleotide that is exonuclease-treated and detected in any way(e.g. run on a gel) is interpreted as meeting this claim limitation. Further, as can be seen on page 4 of the Official Action, "cleaving the cleavable function" is interpreted broadly to be taught by a step of washing under denaturing conditions(see Figure 4 description) which is interpreted as teaching the

broadly claimed and undefined, "cleaving and cleavable function". In response to applicant's second argument regarding their interpretation that " the probes do not contain a solid phase anchor", in the absence of any definition in the specification or claims, the limitation is met by Nilsson's teaching of the probes bound to a slide in the description of Figure 4. In response to applicant's argument regarding the fact that "non-ligated probes are not removed by cleaving the probes because they do not contain a cleavable function". It should be noted that such a requirement for "non-ligated probes" is absent from the claims as written, and as mentioned above, limitations of the specification and arguments cannot be read into the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al.(Science, Vol. 265, pages 2085-2088 September 30, 1994) in further view of Urdea et al.(US Patent 5,124,246).

With regard to claim 22, a cleavable, detectable function is broadly interpreted to include anything that is removable and detectable. For example, a nucleotide that is exonuclease-treated

and detected is interpreted as meeting this claim limitation. Nilsson et al. teaches a method of detecting a target nucleic acid sequence in a sample by contacting the sample with a detectable probe to hybridize the probe to the target sequence, and detecting the hybridized probe, said probe has two free nucleic acid end parts which are at least partially complementary to and capable of hybridizing to two at least substantially neighboring regions of the target sequence (Figure 4 description), comprising the following steps:

a) hybridizing the probe ends to the target sequence under hybridization conditions (Figure 4 description);

b) covalently connecting the ends of the hybridized probe with each other to form a circularized structure;(Figure 4 description)

c) cleaving the cleavable function (e.g. washing under denaturing conditions in this case) (Figure 4), characterized in that the probe is provided with a cleavable or dissociable detectable function (Figure 4 description), and the method comprising the further steps of:

d) separating detectable functions no longer linked to the solid phase (Figure 4 description);

e) detecting the presence and, if desired, location of the remaining probe as indicative of the presence of the target nucleic acid sequence (Figure 4 description).

With regard to claims 26 and 27, Nilsson et al. teaches that the detectable function is dissociable by being provided either on a further circularizable probe or on a target-specific probe (Figure 4 description).

With regard to claim 30, Nilsson et al. further teaches the performance covalent connection of the probe ends by enzymatic or chemical ligation (Figure 4 description).

With regard to claim 31, Nilsson et al. teaches the DNA or RNA as target molecule (Figure 4 description).

With regard to claim 32, Nilsson et al. teaches the immobilization of oligonucleotide probes as well as the target sequence to a solid phase (Figure 4 description).

Nilsson et al. do not teach the detectable function is cleavable by cleaving a cleavable linker located on the same probe end as the detectable function with regard to claim 23.

However, Urdea et al. teach the detectable function is cleavable by cleaving a cleavable linker located on the same probe end as the detectable function (Figures 3-2 and Column 12, lines 49 to column 13, line 43).

Nilsson et al. also do not teach the method with branched or bifurcated probes with regards to claims 24 and 25.

However, Urdea et al. teaches a circularizable probe comprising two free cleavable or detectable nucleic acid end parts which are linear, branched or bifurcated and are capable of hybridizing to two at least substantially neighboring regions of a target sequence (abstract, examples 1, 2 and 3).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the branched or bifurcated probes of Urdea et al. in the method of Nilsson et al. since Urdea et al state, "suitable cleavable linker molecules may be incorporated into the multimers at predetermined sites for the purpose of analyzing the structure of the multimer or as a means for releasing predetermined segments (such as the portion of the multimer that binds to the oligonucleotide) (Column 12, lines 49-55)99. Moreover, Urdea et al. states "The multimers may be used in essentially any of the known nucleic acid

hybridization formats, such as those in which the analyte is bound directly to a solid phase or a sandwich hybridization in which the analyte is bound to an oligonucleotide that is in turn bound to a solid phase (Column 13, lines 56-61)". An ordinary practitioner would have been motivated to combine and substitute the branched or bifurcated probes of Urdea et al. into the method of Nilsson et al. in order to achieve the express advantages, as noted by Urdea et al., of improving the sensitivity of nucleic acid based assay by applying multimers, which may be used in essentially any of the known nucleic acid hybridization formats, such as those in which the analyte is bound directly to a solid phase or sandwich hybridization in which the analyte is bound to an oligonucleotide that is in turn bound to a solid phase.

Response to Arguments

Applicant's arguments filed 11/9/2004 have been fully considered but they are not persuasive. No new arguments are presented in response to this rejection that haven't already been addressed above in response to the 102(b) rejection, applicant should reference the above response.

3. Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al.(Science, Vol. 265, pages 2085-2088 September 30, 1994) in further view of Birkenmeyer et al.(US Patent 5,427,930).

While the teachings of Nilsson et al. are summarized above, the reference does not teach the interspace between probe ends which is filled by an extension reaction prior to covalently interconnecting the probe ends.

However, Birkenmeyer et al. teaches the interspace between probe ends which is filled by an extension reaction prior to covalently inter-connecting the probe ends (abstract and example 1). It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute gap filling ligase chain reaction in the method of Nilsson et al. since Birkenmeyer et al. states "it is therefore a primary object of the present invention to improve the sensitivity of nucleic acid based assay by decreasing the occurrence of target independent ligation which causes falsely positive background signal. This object is met in the present invention by modifying at least one probe end so that when hybridized with its complementary probe, the resulting duplex is not "blunt-ended" (i.e. ligatable) with respect to the partner complementary probe duplexes. After hybridization to the target, the modified ends are "corrected" in a target dependent fashion to render the adjacent probes ligatable. Several features of the probes and the associated target sequences taught in this application makes this task particularly elegant (column 2, lines 28-42)". An ordinary practitioner would have been motivated to combine gap filling ligase chain reaction into the method of Nilsson et al. in order to achieve the express advantages, as noted by Birkenmeyer et al., of improving the sensitivity of nucleic acid based assay by decreasing the occurrence of target independent ligation.

Response to Arguments

Applicant's arguments filed 11/9/2004 have been fully considered but they are not persuasive. Applicant's argue that Birkenmeyer et al. "teach away from the claimed invention" since applicant's invention "are optimally designed to hybridize to a target molecule to leave a small gap between adjacent probe ends". However, as can be read above, applicant cannot read limitations of the specification(e.g. page 4, lines 29-31) into their claims, and this limitation is

not presently recited in applicants claims. As a result the presently cited Birkenmeyer et al. reference is deemed appropriate in light of the presently written claim limitations.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A. Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris
2/4/2005

JEFFREY FREDMAN
PRIMARY EXAMINER
2/5/05